Remarks

Claims 2, 4, 16, 18, 22 and 40 are currently under examination. Pursuant to the following remarks, Applicants respectfully request allowance of the claims to issue.

The present Office Action enumerates eight grounds for why the Examiner believes applicants previous arguments are not persuasive. Applicants previous arguments are hereby re-asserted, and are believed to be responsive to the specific grounds stated by the Examiner in the present Office Action. Furthermore, applicants provide additional reasons why the rejections of the claims recited in the current Office Action and in the previous Office Actions should be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 2, 4, 16, 18, 22 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Li et al. (US Patent No. 6,638,502) in view of Restifo et al. for reasons of record and additional reasons set forth in the Office Action dated November 13, 2008.

The Examiner has responded to Applicants' arguments that "Restifo et al only use the E19 ss to express short peptides" and "there is no evidence that the E19 ss can direct secretion of an heterologous protein" by stating that "Restifo et al. indicate the signal sequence may precede another peptide from 5 to 1000 amino acid residues (column 4 lines 32-40)." The Examiner has also stated that "[p]rior art is presumed to be enabling, absent evidence to the contrary..." The Examiner further asserts that the Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al would be unexpected. Secondly, regarding Applicants' argument that "nothing in the prior art suggest arriving at a composition that reduces tumor growth when administered systemically," the Examiner has asserted that "[t]he composition taught by the prior art meets all the structural limitations of the claims, and thus meets the intended use limitation."

Applicants respectfully traverse. Applicants submit that there is enough unpredictability associated with using the E19 signal sequence that it would be reasonable for one skilled in the art to be surprised that the signal sequence worked in the manner required by the claims. In

particular, there is no evidence in the art that the E3/19K signal sequence from the adenovirus is associated with proteins that are secreted from the cell. Rather, in nature it is a signal sequence for the E3/19K protein whose function appears to be to associate with HLA antigens (also called the MHC [major histocompatibility complex] proteins) within the ER in order to prevent their cell surface expression so that infected cells can avoid being targeted for destruction by T cells due to a lower density of cell surface MHC class I antigens (Gabathuler and Kvist, *J. Cell Biology* 1990; 111:1803-1810). Thus, the literature describing the native E3/19K protein provides no suggestion that the E19 signal sequence could be used with a protein for which secretion is required.

Moreover, the experiments of Restifo (Patent No. 5,733,548) involve targeting enough oligopeptide (i.e. "other peptide") to the ER to associate with the MHC class I molecules in the ER, such that when this complex is then displayed on the cell surface, a T-cell response can be elicited. Proteins associated with MHC class I molecules are not secreted, and those of skill in the art recognize this. Rather, they remain connected to the cell membrane via the MHC class I molecule (Restifo Patent No. 5,733,548 column 1, lines 39-42). Thus, Restifo et al. provides no evidence that the proteins linked to the E19 signal sequence are secreted. Restifo et al. is presumed to be enabled for what it teaches, and it does not teach any secretion of the peptides linked to E19. Thus, contrary to the assertion in the Office Action, the E3/19K signal sequence is not evidenced by the art of record to direct secretion of heterologous proteins.

In fact, none of cited art gives even a hint that proteins attached to the E3/19K signal sequence would be secreted. Thus, Applicants are the first to measure secretion using the E3/19K signal sequence. Because of this, it would be surprising to one skilled in the art that combining E3/19K with an antiangiogenic protein would produce significant secreted (circulating) levels of the protein. Surprising results are necessarily non-obvious.

Li et al. teaches "a signal sequence to direct the secretion of antiangiogenic proteins expressed from the adenoviral vectors (see the Examples), one of which, angiostatin, targets endothelial cells" (from the November 11, 2006 Office Action), and that signal sequence is not the E3/19K signal sequence. This teaching of Li et al. fails to provide the information needed to make an obviousness rejection that is missing from Restifo et al., namely it fails to suggest that

the E3/19K signal sequence permits secretion of the protein it is linked to. For this reason alone, the recited combination of references fails to make out a prima facie case of obviousness of the present claims.

The present rejection appears to be based on the presumption that all signal sequences are alike in their effect on secretion of the proteins they are attached to. The scientific literature contradicts this assumption. In fact, there is still uncertainty in the scientific literature regarding how well signal sequences perform in targeting their linked proteins to the secretory pathway. For example, it has been stated that "signal peptide efficiency can vary considerably in different cell types," (Hegde and Bernstein, *TRENDS in Biochemical Sciences* 2006; 31:563-571). Also Martoglio et al. (cited by the Examiner) states that "[s]ignal sequences can differ in the efficiency by which they mediate targeting and membrane insertion." Such unpredictability is further evidence that secretion of large amounts of protein, as in the present case, is a surprising result. Neither Restifo et al. nor Li et al. provide evidence that supports any notion that E3/K19 would predictably produce high levels of secreted anti-antiogenic protein. Therefore, the state of the art at the time of the present invention was that signal sequences vary in their effect on the secretion of proteins they are attached to, and the cited art does not modify the state of the art. Thus, it can be easily understood why one skilled in the art would be surprised that the E3/19K signal sequence produced increased circulating levels of the protein sufficient to inhibit tumor growth, especially when there were no previous secretion data for E3/19K. Also, because Li et al. only performed intratumoral work, and because Griscelli et al. did not use a construct that is closely structurally related to the present construct, there is no evidence of increased circulating levels. Such unpredictability exists in this case and is further evidence of surprising results.

Applicants also respectfully submit that the recitation that "systemic delivery results in increased circulating levels" in claim 40 refers to the composition and is a functional limitation. A functional limitation defines the composition of matter, by requiring that it exhibit a recited function. A functional limitation can exclude from a claim compositions that would otherwise be covered by the claim. The statement that "systemic delivery" of the claimed composition "results in increased circulating levels of the antiangiogenic protein and inhibition of tumor growth" is not a mere statement of intended use but a functional limitation that restricts the claimed compositions to those having the recited function. Such a functional limitation would

potentially exclude compositions that have the recited structural elements but not the functional elements. Therefore, a functional limitation defines the scope of the claimed composition and must be treated as a claim limitation for the purpose of an analysis under section 103 of the patent statute. By categorizing the recited functional limitation as merely an intended use, the Examiner has discounted the importance of this function in the determination of whether one of skill in the art would or would not have a reasonable expectation of success. The fact that a functional limitation may also imply an intended use, does not alter the fact that it also defines the composition. Applicants respectfully assert that the if the functional limitation is given proper weight, the analysis results in a conclusion that the combination of Li et al. in view of Restifo et al. does not suggest a composition that has the structural and functional limitations of the pending claims, including increased circulating levels upon systemic delivery. Applicants therefore respectfully request withdrawal of this rejection.

Applicants submit that there is no reasonable expectation of success when using the E3/19K signal sequence linked with a large heterologous protein targeted for secretion, and that claim 40 is suitable for issuance. Therefore, for the reasons set forth above, Applicants believe that claims 2, 4, 16, 18, 22 and 40 are unobvious over Li et al. in view of Restifo et al. Thus, Applicants respectfully request withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment submitted via EFS Web in the amount of $130.00, representing the fee for a large entity under 37 C.F.R. § 1.17(a)(1), and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629

Respectfully submitted,

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